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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/534,706	03/24/00	ELLMAN J	18062G002010

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TOWNSEND AND TOWNSEND AND CREW
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EIGHTH FLOOR
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EXAMINER	
MCKENZIE, T	
ART UNIT	PAPER NUMBER
1624	5

DATE MAILED: 05/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/534,706	ELLMAN ET AL.	
	Examiner	Art Unit	
	Thomas C McKenzie,Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is in response to an application filed on 3/24/00. There are fifty claims pending and under consideration. Claims 1-50 are use claims. This is the first action on the merits. The application concerns some peptide mimetic enzyme inhibitors.

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Abstract

3. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and 18-50 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well-established

utility. Applicants' only assertion of a specific and substantial utility is to treatment of Alzheimer's Disease. Wagner (J. Clinical Invest.) in the first sentence of the paragraph spanning both sides of page 1332 makes clear that the *in vivo* evaluation of modulators of β-amyloid production has not been done. In the final sentence Wagner (J. Clinical Invest.) writes "none of the currently available models recapitulate the entire scope of behavioral and pathaological features of [Alzheimer's Disease]". Thus, not only have Applicants' compounds been evaluated for clinical efficacy, no compounds which share Applicants' mechanism of action been evaluated for such human effacy. In addition, there is no demonstration of correlation of *in vitro* data to human effacy in this area.

5. Claims 1-17 and 19-50 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claim 18 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Claim 18 is drawn to increasing amyloid production. The specification fails to make clear the benefit of this. Since such an action would

exacerbate the symptoms of Alzheimer's Disease, such a use would lack a well-known utility as well as lack an asserted utility.

7. Claim 18 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. Claims 36-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of "neurodegenerative disorders" cannot be deemed enabled. The term "neurodegenerative disorders" covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; Gerstmann-Straussler-Scheinker Disease (GSS); Pick's Disease; Diffuse Lewy Body Disease; Hallervordon-Spatz disease; progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration; progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and

Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmotic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); retinitis pigmentosa; Leber's Disease; and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give progressive dementia without other prominent neurological signs, such as Alzheimer's Disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some are abnormalities of posture, movement or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's Disease and FTDP-17, and other such as Parkinson's clearly do not. Some affect only vision such as retinitis pigmentosa. Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's Disease and Pick's disease

both give progressive dementia without other prominent neurological signs. But the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's Disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's Disease. There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are different. Thus, FTDP-17 comes from chromosome 17, Huntington's Disease from 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to 21.

The great majority of these have no treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. The great diversity of diseases falling within the "neurodegenerative disorder" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. In Olson (Annual Reports in Medicinal Chemistry) dated 2000 possible therapeutic applications secretase

inhibitors is discussed. On page 37, last sentence, reports that γ-secretase inhibitors "are approaching clinical evaluation" makes clear that no such evaluation has been completed and there is no evidence of clinical efficacy.

The scope of "treating ... cognition disorders" cannot be deemed enabled. The term "cognition" covers uses on a broad array of human mental states. It would encompass both normal subjects as well as patients suffering from various disorders that have different modes of action and different origins. These disorders would include developmental dyslexia, closed head injury, schizophrenia, Alzheimer's disease, mild cognitive disorder, sub-clinical senescent cognitive disorder, and depression. Most of these disorders have no effective treatment at all, and none have been treated with such inhibitors as are disclosed here.

The scope of "treating ... Alzheimer's disease" cannot be deemed enabled. There is no cure for the different types of Alzheimer's diseases and none have been treated with such amyloid modulators as are disclosed here. Wagner (J. Clinical Invest.) in the first sentence of the paragraph spanning both sides of page 1332 makes clear that the *in vivo* evaluation of modulators of β-amyloid production has not been done. In the final sentence Wagner (J. Clinical Invest.) writes "none of the currently available models recapitulate the entire scope of behavioral and pathaological features of [Alzheimer's Disease]". Augelli-Szafran (Ann. Reports

Med. Chem.) writes in the final two sentences of the first paragraph on page 28, "question that remains to be answered is whether compounds that inhibit [amyloid β] production ... will impede the pathogenesis of [Alzheimer's Disease]." Thus, as of 1999 clinical effacay of compounds with Applicants' mechanism of action had not been established.

The intractability of Alzheimer's disease is clear evidence that the skill level in this art is low relative to the difficulty of the task and not sufficient to enable treatment with inhibitors of this sort. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's diseases has produced are means of providing acetylcholinesterase inhibition, unrelated to the mechanism of action in this case.

The scope of "treatment or preventing ..... Parkinson's diseases" cannot be deemed enabled. A recent review "Developments in the Treatment of Parkinson's Disease" mentions levodopa, catechol-O-methyl transferase inhibitors, dopamine agonists, muscarinic antagonists, and N-methyl-D-aspartate receptor antagonists as possible therapeutic modalities for Parkinson's disease. The review does not mention such inhibitors as are disclosed here.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the line immediately above the formula (I) in claims 1, 19, and 36 the word "general" occurs. This is indefinite for it implies other formulas are being claimed as well. The Examiner suggests deleting the word.

10. The final formula in claim 6, the last two formulas in claim 23, and the final formula in claim 43 have a double bond drawn to a CH_2 group and a second bond emanating from the CH_2. Since we do not know if a single bond or a CH group was intended, clarification is required.

11. Applicants repeatedly claim "substituted alkyl", "substituted aryl", and "substituted heteroaryl". These terms are defined in the specification in lines 9-15, page 11, lines 25-32, page 11, and lines 13-22, page 13 respectively. The definitions use open language "such as" are there any limitations as to which substituents are claimed? "Heterocycles" are defined to contain only carbon, nitrogen, oxygen, and sulfur. Do these same limitations apply to "heteroaryl"?

12. Claims 1-15, 18-33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word

"modulating" in claim 1 and in claim 19 is indefinite. Webster's lists six meanings for modulate. The first definition, "to regulate, adjust, or adopt" does not specify what is to be adjusted. The other five definitions concern frequency. Adjust could mean speed up or slow down. It could mean increase the amount or decrease the amount. If the "processing of an amyloid precursor protein" does not occur at a steady rate, but rather a varying rate, "modulating" could have a frequency meaning, i.e. the second derivative, not the first derivative, of the amount of APP. What is Applicants' intended meaning?

Conclusion

13. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

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May 22, 2001